

REMARKS

TELEPHONE INTERVIEW ON JULY 7, 2004

Applicants thank the examiner for the courtesies extended during the telephone interview of July 7, 2004. On the phone for Applicants for the interview were Melodie Henderson, Sandra
5 Shaner and inventor Richard Judson. Discussion was focused on clarifying aspects of the rejections of the claims under 35 USC §101 and 35 USC §112.

INFORMATION DISCLOSURE STATEMENT

The Office Action states that the Form PTO-1449 for the information disclosure statement submitted June 12, 2003 has only one page, and the upper right hand corner of that page suggests
10 that there should be a total of six pages since it says "Page 1 of 6". Attached herewith is a copy of the postcard showing receipt of the Form PTO-1449 and the 162 references by the USPTO based on the OIPE date stamp of June 12, 2003 as well as a copy of the missing pages 2-6 of the Form PTO-1449.

AMENDMENTS TO THE SPECIFICATION

15 The specification is amended on p. 1 to correct the information relating the current application to earlier applications.

Additionally, the specification is amended to correct an obvious typographic error in a figure number on p. 145.

AMENDMENTS TO THE CLAIMS

20 Claim 59 is amended to clarify the language of the claim. Support for these amendments is found in the claim as filed and in the specification at p. 30, lines 17-20; p. 64, lines 29-30; p. 64, line 35 to p. 65, line 1; p. 65, lines 4-6, line 22 and lines 25-32; p. 66, lines 14-32; p. 67, lines 9-10; and p. 152, line 21-23. In particular, support for amendments in step (a) is found in the claim as filed and in the specification at p. 30, lines 17-20; p. 64, lines 29-30; p. 64, line 35 to p. 65, line 1;
25 p. 65, line 22; p. 65, lines 4-6; and p. 152, line 21-23.

Claims 60-63, depending from claim 59, are also amended. Support for the amendments is found in the specification at p. 65, lines 27-33; p. 144, lines 1-2; claims 112 and 113, as filed; Fig. 45 (S14); p. 67, lines 2-6.

5 Claims 110-114 and claims 161-165 are amended to be consistent with the language of the method of amended claims 59-63.

Claim 64 is amended to clarify the language of the claim. Support for these amendments is found in the claim as filed and in the specification at p. 67, lines 19-26 and lines 29-31; p. 68, lines 11, 15 and 19-20; and p. 152, line 21.

10 Claims 65-68, depending from claim 64, are also amended. Support for the amendments is found in the specification at p. 68, lines 15-25; p. 69, lines 15-22.

Claims 115-119 and claims 166-170 are amended to be consistent with the language of the method of amended claims 64-68.

15 New claims 184 and 185 depend from claims 59 and 60, respectively. New claims 186 and 187 depend from claims 64 and 65, respectively. Support for claims 185 and 187 is found in Figure 39A. Support for claim 184 is found in the specification at p. 64, line 30-32 and p. 65, lines 4-6. Support for claim 186 is found in the specification at p. 67, lines 19-21 and lines 29-31.

20 New independent claim 188 and dependent claims 189-190 are also added. Support for claims 188-190 is found in claim 59, as filed, and in the specification at p. 30, lines 17-20; p. 64, lines 29-32; p. 64, line 35 to p. 65, line 1; p. 65, line 22; p. 65, lines 4-6 and lines 25-32; p. 66, lines 14-24; p. 66, lines 25-32; and p. 67, lines 9-10; p. 152, line 21-23; p. 153, lines 21-22; and Figure 39A.

Applicants respectfully submit that the new claims are directed to the elected subject matter, and thus their entry for substantive examination is requested.

25 Applicants believe that, despite a net loss in the total number of claims after amendment, they owe fees for the added independent claim, and hereby authorize you to debit deposit account 50-1293 for these claim fees, as stated on the attached fee transmittal form.

OBJECTIONS UNDER 37 CFR 1.75(C)

30 The Office Action objects to claims 114 and 119 under 37 CFR 1.75(c) as being multiple dependent claims in improper form for failing to refer to the claims from which each depends in the alternative. Claims 114 and 119 are amended herein to depend from a single claim.

Applicants request withdrawal of the objections to amended claims 114 and 119 and examination of these claims on the merits.

REJECTIONS UNDER 35 USC §101

The Office Action rejects claims 59-68 under 35 USC §101, stating that claims 59-68 are directed to non-statutory subject matter "as the methods merely manipulate data and do not produce a tangible, concrete and useful result." Applicants believe that the Office Action has failed to establish a *prima facie* case that the claimed invention is directed to non-statutory subject matter. The Office Action fails to provide any support that the claimed invention as a whole is directed to an abstract idea or to manipulation of abstract ideas or does not produce a useful result.

For a method to meet the standards of statutory subject matter under 35 USC §101, the "claimed invention as a whole must accomplish a practical application" (MPEP §2106A), i.e., it must produce a "useful, concrete and tangible result." (See *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368 (Fed. Cir. 1998); *AT&T Corp v. Excel Communications, Inc.* 172 F.3d 1352 (Fed. Cir. 1999)). The proper inquiry in dealing with so-called mathematical subject matter according to *In re Alappat* 33 F.3d 1526 (Fed. Cir. 1994) is "to see whether the claimed subject matter as a whole is a disembodied mathematical concept,...which in essence represents nothing more than a "law of nature", "natural phenomenon", or "abstract idea". If the claimed invention produces a "useful, concrete, and tangible result", the invention is directed to statutory subject matter according to *In re Alappat*. *AT&T Corp v. Excel Communications, Inc.* 172 F.3d 1352 (Fed. Cir. 1999) summarized the *Alappat* test as follows: "to see if the claimed subject matter as a whole is a disembodied mathematical concept representing nothing more than a "law of nature" or an "abstract idea," or if the mathematical concept has been reduced to some practical application rendering it "useful."

Independent claims 59 and 64 are each directed to a method of determining polymorphic sites or sub-haplotypes that correlate with an outcome of interest. The inventions of amended claims 59-68 do not merely manipulate abstract concepts or ideas without some practical application. In *State Street*, data representing discrete dollar amounts were mathematically converted into a final share price. The inventions of amended claims 59-68 are similarly a practical application of an algorithm in the technological arts as the claimed processes include steps of providing haplotypes and outcome values for the outcome of interest for each subject in a cohort of subjects, analyzing individual polymorphisms and subhaplotypes within the haplotypes

for statistical correlation with the outcome, and saving each individual polymorphism and sub-haplotype whose degree of correlation meets a cut-off criterion and its numerical measure of the degree of correlation. The outcome of interest may be a clinical outcome, e.g. drug response, or it may be another phenotype, e.g., ability of an animal to provide more lean meat. The

5 polymorphisms and sub-haplotypes correlated with the outcome that are saved, for display or future use, are a useful, concrete and tangible result of performing the claimed methods. For example, if the outcome of interest is drug response, disease susceptibility or disease progression, these correlated polymorphisms and sub-haplotypes are useful in a variety of applications known to the skilled artisan in the fields of drug development and treatment. Applications mentioned in the

10 specification include developing tests to predict drug response or establishing patient eligibility criteria for phase II and phase III clinical trials (see, e.g.: p. 1, lines 15 to 19; p. 30, lines 10-12; p. 135, lines 21 to 26; p. 136, lines 17 to 26.)

Since the claimed methods of amended claims 59-68 are practical applications within the technological arts and do produce a useful, concrete and tangible result, amended claims 59-68 are

15 directed to statutory subject matter. Applicants therefore request reconsideration and withdrawal of the rejection of amended claims 59-68 under 35 USC §101.

REJECTIONS UNDER 35 USC §112, 1ST PARAGRAPH

The Office Action rejects Claims 59-68, 110-113, 115-118 and 161-170 under 35 USC

20 §112, 1st paragraph as "failing to comply with the enablement requirement." This conclusion is based on several allegations, which may be grouped into three categories: (a) "the claims as written are incomplete with respect to exactly what is input, what is processed and how, what specifically is saved, and what information is output", (b) the methods generate "information that is not meaningful to those of ordinary skill in the art", and (c) "the specification discloses no

25 databases readily available to the public containing the information required by the claims" and that producing such a database would require undue experimentation".

Applicants assert that the Office Action fails to establish a *prima facie* case of lack of enablement of claims 59-68, 110-113, 115-118 and 161-170 under 35 USC §112, 1st paragraph. The test for enablement of a claimed invention is "whether one reasonably skilled in the art could

30 make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation". *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988). The

specification need not be a blueprint to satisfy the enablement requirement. *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (Bd Pat. App. & Int. 1992). Indeed, the specification may omit details which are well-known in the art. *See, e.g., In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). Moreover, claims that encompass some inoperative embodiments are valid and enabled if
5 the skilled artisan can choose operative from inoperative embodiments without undue experimentation. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984).

Claims 59-68 are directed to methods for determining polymorphic sites or sub-haplotypes for a locus that correlate with an outcome of interest. As would be evident to the skilled artisan
10 from reviewing the specification and figures, the inputs for these methods are haplotype and outcome data, the composition of which are clarified in amended independent claims 59 and 64. These data are processed according to steps (b) to (h), which are amended to clarify, *inter alia*, what is statistically analyzed (steps (b) and (e)), which polymorphisms and sub-haplotypes are saved along with their numerical measure of the degree of correlation (steps (c) and (e)) and what
15 is done with these saved polymorphisms and sub-haplotypes (steps (d), (g) and (h)).

In alleging that the claims as originally filed were incomplete, the Office Action states "to accomplish the goals of the method more information must be retained than that required by the claim". However, the Office Action fails to provide an example of what additional information must be retained to accomplish the method's goal of determining polymorphic sites or sub-
20 haplotypes for the locus that correlate with the outcome of interest. Amended independent claim 59 recites saving each polymorphism and sub-haplotype that is correlated with the outcome of interest to a degree that meets a cut-off criterion as well as its numerical measure for the degree of correlation. Amended independent claim 64 recites saving each haplotype and sub-haplotype that is correlated with the outcome of interest to a degree that meets a cut-off criterion along with its
25 numerical measure for the degree of correlation. Applicants assert that no other information needs to be saved to achieve the goal of these methods.

The Office Action states that the claims as filed are also incomplete with respect to how the input data is processed. The two types of processing performed in amended claim 59 are statistically analyzing each polymorphism or generated sub-haplotype for the degree to which it
30 correlates with the outcome of interest (steps (b) and (e)) and generating all possible pair-wise combinations of the saved polymorphisms and/or sub-haplotypes (steps (d) and (g)). Similarly, the two types of processing performed in amended claim 64 are statistically analyzing each

haplotype or generated sub-haplotype for the degree to which it correlates with the outcome of interest (steps (b) and (e)) and generating all possible sub-haplotypes resulting from systematically masking a polymorphic site in the saved haplotype (step (d)) or sub-haplotype (step (g)). With respect to how the statistical analysis steps are performed, Applicants note that the specification, at p. 65, lines 16-24 and p. 68, lines 5-14, mentions several types of statistical analysis that might be chosen for analyzing the degree of correlation of individual polymorphisms, haplotypes or sub-haplotypes with the phenotype of interest, and includes a more extensive discussion of statistical analyses to find such correlations at p. 48, line 3 to p. 53, line 4.

In support of its allegation that the methods generate "information that is not meaningful to those of ordinary skill in the art", the Office Action states that "the cut-off values are not specified" for the degree of correlation. Applicants assert that the skilled artisan could choose, using the guidance provided in the specification combined with what was known in the art and no more than routine experimentation, statistical parameters to use for the degree of correlation and values for the cut-off criterion that would generate correlated haplotypes, subhaplotypes and individual polymorphisms that would be meaningful for the artisan's intended use of such correlated markers. For example, Applicants note that cut-off criteria and cut-off values, using p-values as the measure for degree of correlation, are explicitly discussed in the context of the methods of claims 59 and 64 in the specification at p. 65, lines 25-34 and at p. 68 lines 15 to 26. Additionally, other statistical test parameters that might be used to measure the degree of correlation are discussed in the specification at p. 48, line 3 to p. 53, line 4 and Figures 18-23. For example, Fig 23 presents a display of an ANOVA analysis discussed at p 52, line 6 to p. 53, line 4 in which an F ratio was used to gauge the degree of correlation, and values of the F statistic corresponding to confidence levels of 90%, 95% and 99% are displayed for comparison to the F ratio for that particular analysis.

The Office Action also supports its allegation that the claimed method could produce unmeaningful information with the statement that the "claims don't speak to size or composition of the cohort such that statistically valid results are produced, comparison of like information, and so forth." Amended claims 59 and 64 clarify that an outcome value for the outcome of interest is provided for each subject in the cohort. Applicants note that the specification provides, on p. 47, lines 5-31 and p. 142, lines 26-28, guidance on the composition of the cohort for the particular example of applying the methods of claims 59-68 to a clinical outcome. Applicants assert that the skilled artisan could choose, using the guidance provided in the specification combined with what

was known in the art and no more than routine experimentation, an appropriate size or composition of the cohort and an appropriate outcome of interest that would produce meaningful results from the claimed method for the artisan's intended use. With regard to the size of the cohort, Applicants note that Example 2 of the specification describes applying the claimed

5 methods to a cohort of 134 asthma patients who were treated with albuterol to identify genetic markers that are correlated with the response to albuterol to a statistically significant degree. Further, Applicants assert that sample size or power calculations could be done by a trained statistician before the filing date of this application in order to determine the size of a cohort required to obtain meaningful results from a statistical analysis for a particular phenotype.

10 Standard methods existed in the art for performing such power calculations for normally distributed data and other types, including dichotomous data, with three inputs known to be necessary: expected or desired effect size, significance level and sample size ratio (corresponding to expected marker group frequency). For example, a statistics text referenced in the specification on p. 147, Fisher and VanBelle's "Biostatistics: A Methodology for the Health Sciences"

15 published in 1993, discusses such calculations to determine sample size at pp. 158-161 (attached herewith) and also in chapter 17 (pp 844-862).

Finally, the third allegation the Office Action makes in finding lack of enablement of claims 59-68 is that "the specification discloses no databases readily available to the public containing the information required by the claims" and that to produce such a database would

20 require undue experimentation of one of ordinary skill in the art since it would require exercising inventive skill and judgment to "determine what information to include and exclude and in what form to compile the information decided upon for statistical analysis". Since claims 59-68 do not recite a database, Applicants presume this allegation refers only to claims 110-119 and 161-170. Applicants note that the specification at p. 142, line 24 to p. 146, line 9 provides an example of

25 determining individual polymorphisms and sub-haplotypes of the ADRB2 gene associated with response to an asthma drug that included using the claimed inventions (Example 2). Figures 28 and 29 referred to in Example 2 provide examples of the polymorphism, haplotype and phenotypic data used as inputs for performing the methods claimed in amended claims 59 and 64. Thus, Applicants believe that the specification enables determination of what information should be

30 included in a database for amended claims 110-119 and 161-170. Applicants assert that deciding on a form for the database of information for the statistical analysis was within the skill of the practitioner at the time of filing the application and note that the specification states on p. 26, lines

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27-29 that the data processed by the disclosed inventions may be stored in a set of ASCII flat files or using the commercially available software Oracle® Database. In addition, the specification provides an extensive description on p. 71 to p. 128 of database models for efficiently storing and searching genomic and clinical information. The skilled practitioner would have known that data
5 utilized in the invention claimed in claims 110-119 and 161-170 might be organized in these forms, and that multiple commercial programs of varying sophistication were available that might alternatively be used to organize the information, such as Microsoft® Excel, Microsoft® Access or Oracle® Database.

For the above stated reasons, Applicants request reconsideration and withdrawal of the
10 rejection of Claims 59-68, 110-113, 115-118 and 161-170 under 35 USC §112, 1st paragraph.

REJECTIONS UNDER 35 USC §112, 2ND PARAGRAPH

The Office Action rejects Claims 59-68, 110-113, 115-118 and 161-170 under 35 USC §112, 2nd paragraph as being indefinite for failing to particularly point out and distinctly claim the
15 subject matter which applicant regards as the invention.

In particular, the Office Action rejects claims 59, 110, 112, 161 and 163 for reciting “(clinical outcome values)”, stating that it is unclear whether this parenthetical phrase is a specific limitation of the claims. Claims 59, 110, 112, 161 and 163 are each amended to eliminate use of this parenthetical phrase and to make consistent within each claim, use of the term “outcome
20 value”.

The Office Action rejects at least claims 63 and 68 for reciting “complex subhaplotypes”, stating that it is unclear what the metes and bounds are for this phrase. Claims 63, 68, 114 and 165 are amended to recite “complex redundant sub-haplotypes” which are described in the specification on p. 67, lines 2-6.

25 The Office Action states that claims 59, 64, 110, 112, 115, 117, 161, 163, 166 and 168 appear to require an “and” inserted between parts (g) and (h). Claims 59, 64, 110, 112, 115, 117, 161, 163, 166 and 168 are amended to insert an “and” between parts (g) and (h).

The Office Action notes a typographical error in claim 66, i.e. the word “fi3st”. This typographical error is amended herein to read “first”.

30 The Office Action rejects claims 110-113, 115-118 and 161-170 for being unclear as to whether each portion of the computer-readable code are sections of a single program, separate

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programs, or something else. The Office Action further notes that these claims don't make clear any relationship between the program code of the subparts, citing the example that it is unclear if the code must be executed in a particular order. Claims 110-113, 115-118 and 161-170 are herein amended to clarify that the program code must execute the recited steps of a method.

5 For the above stated reasons, Applicants request reconsideration and withdrawal of the rejection of Claims 59-68, 110-113, 115-118 and 161-170 under 35 USC §112, 2nd paragraph.

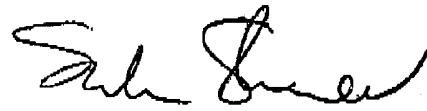
Should any questions arise, or if Applicants or Applicants' Agent can facilitate examination of this application, it is respectfully requested that the undersigned Agent be
10 contacted so that any remaining issues can be resolved.

Respectfully submitted,

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Case No. 2458-4042US5 Serial No. 10/019,342
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